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Original Article

Beneficial effect of early initiation of lipid-lowering therapy following renal transplantation

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Abstract

Background. Renal transplant recipients have a significantly reduced life expectancy, largely due to premature cardiovascular disease. The aim of the current analysis was to investigate the importance of time of initiation of therapy after transplantation, on the benefits of statin therapy.

Methods. 2102 renal transplant recipients with total cholesterol levels of 4.0–9.0 mmol/l were randomly assigned to treatment with fluvastatin ($n = 1050$) or placebo ($n = 1052$) and followed for a mean time of 5.1 years. The end-points were major cardiac events. The average median time from transplantation to randomization was 4.5 years (range: 0.5–29 years).

Results. In patients starting treatment with fluvastatin <4.5 years after renal transplantation, the incidence of cardiac events was 4.6% over 5.1 years *vs* 9.2% in those on placebo ($P = 0.007$). Fluvastatin significantly reduced the risk of cardiac death and non-fatal myocardial infarction by 56% [risk ratio (RR): 0.44; 95% confidence interval (95% CI): 0.26–0.74; $P = 0.002$]. In a more detailed analysis patients were grouped into 2-year intervals (since the last transplantation). The frequency of cardiac death and non-fatal myocardial infarction was reduced by 3.2%, 5.1%, 9.6% and 8.2% with fluvastatin treatment as compared to 6%, 10.4%, 13.4% and 9.6% with placebo when treatment was initiated at 0–2, 2–4, 4–6 and >6 years, respectively. The risk reduction for patients initiating therapy with fluvastatin at years 0–2 (compared with >6 years) following transplantation was 59% (RR: 0.41; 95% CI: 0.18–0.92; $P = 0.0328$). This is also reflected in total time on renal replacement therapy: in patients in the first quartile (<47 months) fluvastatin use was associated with a risk reduction of 64% compared with 19% for patients in the fourth quartile (>120 months) ($P = 0.033$).

Conclusions. Our data support an early introduction of fluvastatin therapy in a population of transplant recipients at high risk of premature coronary heart disease.

Keywords: cardiac end-points; fluvastatin; renal transplant recipients

Introduction

Renal transplant recipients have a significantly reduced life expectancy, largely due to premature cardiovascular disease [1–3]. Many transplant recipients have pre-existing cardiovascular disease at the time of the transplantation, while immunosuppressive therapy may aggravate existing risk factors or promote the development of new ones, especially hyperlipidaemia and hypertension [4]. Lipid-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) has been shown to significantly reduce the incidence of cardiovascular events. Outcome trials of statin therapy have demonstrated significant reductions in cardiovascular morbidity and mortality, in both primary and secondary prevention populations [5–10], a benefit that emerges ~12 months after initiation of treatment.

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In addition, in recent years, prospective and retrospective studies have indicated that statin therapy should start immediately after an acute event [e.g. myocardial infarction (MI)] in patients with established coronary heart disease [11,12]. More recently, some studies have suggested that the benefit of statin therapy is independent of the level of baseline cholesterol [9,10], although this is not a universal finding [12].

In the ALERT Study [13], we found that treatment with fluvastatin reduced the incidence of major adverse cardiovascular events (cardiac death, non-fatal MI and coronary revascularizations) by 17% in renal transplant recipients. Although the primary end-point did not achieve statistical significance, also due to lower than anticipated rates of coronary revascularization in the study population, this positive trend was supported by a pre-specified, secondary end-point analysis that included non-fatal MI and cardiac death. The risk of cardiac death or definite non-fatal MI was reduced significantly, by 35% [13]. A further finding of the ALERT Study, of major clinical importance, was to demonstrate the safety and efficacy of fluvastatin when administered together with immunosuppressive therapy and a wide range of cardiovascular medication in renal transplant recipients.

The current post-hoc analysis aimed to establish the influence of the time since transplantation, prior to initiation of statin therapy, on the beneficial effects of fluvastatin therapy on cardiac death and non-fatal MI.

Subjects and methods

The ALERT Study design and baseline data have been described previously [14].

Briefly, ALERT recruited 2102 renal transplant recipients from nephrology units and transplant clinics in Northern and Central Europe (Belgium, Denmark, Finland, Germany, Norway, Sweden, Switzerland and the United Kingdom) and Canada. Male and female patients, aged 30–75 years, who had received a renal (or combined renal and pancreas) transplant >6 months prior to randomization, with stable graft function and with total serum cholesterol concentration between 4.0 and 9.0 mmol/l, were recruited. Patients with a history of MI >6 months prior to randomization could be enrolled if their total cholesterol levels ranged from 4.0 to 7.0 mmol/l. Narrower total cholesterol ranges for inclusion were used, if necessary, to satisfy the requirements of local ethics committees. Patients were excluded if they were on statin therapy or had a total cholesterol >9 mmol/l (>7 mmol/l if previous MI), had familial hypercholesterolaemia or had experienced an acute rejection episode in the 3 months prior to randomization or a hospital-verified infarction <6 months prior to randomization. Patients with a predicted life expectancy of <1 year were also excluded. In addition, patients with elevated liver function tests were excluded.

The study adhered to the International Conference on Harmonisation guidelines for Good Clinical Practice and in accordance with the Declaration of Helsinki. All participants provided written informed consent and the ethics committee at each participating centre approved the trial.

Trial procedure

Patients were initially randomized to receive either fluvastatin, 40 mg/day (Lescol®; Novartis Pharma AG, Basel, Switzerland), or matching placebo. After ~2 years, the dose of the study drug was doubled for both groups after obtaining written informed patient consent. The dose increase was implemented on the recommendation of the independent Data and Safety Monitoring Board [13] and based on emerging safety data and clinical outcome trials published after the design of ALERT that provided additional information on the relationship between achieved low-density lipoprotein (LDL)-cholesterol levels and reduction of cardiovascular events. Patients were followed up for a minimum of 5 and a maximum of 6 years. Study patients were seen at 1.5 months following randomization and at 6-month intervals thereafter [14].

End-point definition

The present report is a post-hoc analysis of the main study, which was performed to evaluate the incidence of major cardiac end-points (cardiac death or definite non-fatal MI; primary end-point of the WOSCOP Study [5]) and the effect of the interval between the last transplant and initiation of fluvastatin treatment. An adjudicated MI was classified as definite if a new Q-wave developed in the presence of abnormal cardiac markers or typical/atypical symptoms, or if pathological ST-elevations and T-wave changes developed in the presence of abnormal cardiac markers and typical/atypical symptoms. All deaths were considered cardiac unless an unequivocal non-cardiac cause could be established.

Statistical analysis

In order to assess the potential impact of the interval between transplantation and recruitment to the trial, we categorized the population into subgroups determined by this time interval. Analyses were performed in subgroups divided by the median (4.5 years), in subgroups (0–2, 2–4, 4–6 and >6 years) of time since transplantation. The original sample size calculation was performed assuming a 25% placebo Major Cardiac Event rate after 5 years' follow-up and a 25% effect size. Using the chi-square test statistic for a difference between two proportions, 1476 (738 per group) patients would give a power of ~83% to detect a difference between groups using a two-sided test of size $\alpha = 0.05$. Due to a lower than expected incidence rate, the dose of fluvastatin was doubled and the sample size increased from 1700 to about 2100. Event rates for the end-points described above are presented by groupings. The Cox proportional hazards model was used to generate risk ratios (RR) (fluvastatin/placebo) for the event rates and 95% confidence intervals (95% CI) for those RR. All analyses were carried out using SAS version 8 software.

Results

Between June 1996 and October 1997, 2102 patients were randomly assigned to receive either fluvastatin

($n = 1050$) or placebo ($n = 1052$). All eligible patients were randomized and follow-up was sought for all patients who were withdrawn early from the study. The groups were well balanced with regard to baseline demographic and clinical characteristics, as described previously [2]. Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II blockers were used by 50% and β-blockers by 60% of the patients; however, there was no difference between the groups enrolled before or after 4.5 years. More detailed baseline demographics, including traditional and transplant-related risk factors, are shown in Table 1. Baseline cholesterol and LDL-cholesterol were comparable between patients enrolled in the trial <4.5 *vs* >4.5 years after transplantation. The effect of fluvastatin on LDL- and total cholesterol in both groups was comparable; absolute reduction in LDL-cholesterol was 1.12 (0.0036) *vs* 1.11 (0.038) in patients transplanted <4.5 *vs* >4.5 years prior to study entry. Figure 1 provides in detail the lipid levels throughout the study, showing a similar effect independent of the time-point of entry into the study. The mean duration of follow-up was 5.1 years (SD 1.1); the median follow-up was 5.4 years (interquartile range: 5.2–5.6). The median time since last transplantation was 4.5 years (mean: 5.5 years).

In patients who initiated fluvastatin treatment during the first 4.5 years after the transplant, the incidence of cardiac death and non-fatal MI was 24 out of 522 (4.6%) in the fluvastatin arm and 48 out of 521 (9.2%) in the placebo arm. The risk of cardiac death and non-fatal MI was reduced by 56% (RR: 0.44; 95% CI: 0.26–0.74; $P = 0.002$) as compared with the corresponding placebo controls. There was a consistent pattern of benefit favouring fluvastatin among the individual components with a non-significant 39% risk reduction for cardiac death and a significant 56% reduction in the risk of non-fatal MI (Figure 2). The cumulative rate (Kaplan–Meier event rates) for cardiac death and non-fatal MI is shown in Figure 3.

To evaluate the impact of early fluvastatin therapy following transplantation on the risk of dying of cardiac disease or suffering from non-fatal MI, the study population was divided by 2-year intervals from the last transplant.

In placebo controls, the risk of cardiac death and non-fatal MI was higher in the first 6 years following transplantation (Figure 4). The frequency of cardiac death and non-fatal MI was 3.2%, 5.1%, 9.6% and 8.2% with fluvastatin treatment as compared to 6%, 10.4%, 13.4% and 9.6% with placebo when therapy was initiated at 0–2, 2–4, 4–6 and >6 years after the last transplant, respectively (Figure 4).

Renal function assessed by serum creatinine did not differ throughout the study for patients on placebo *vs* active treatment recruited either early or late into the trial (Figure 5).

Table 1. Demographic data on the study population by time since last transplantation. Data are shown as means (SEM) or % total, as described

	<4.5 years after transplantation ($n = 1044$)[a]		>4.5 years after transplantation ($n = 1058$)[a]	
	Placebo ($n = 521$)	Fluvastatin ($n = 522$)	Placebo ($n = 531$)	Fluvastatin ($n = 527$)
Demographic and clinical characteristics				
Age (years)	49.8 (0.5)	49.0 (0.5)	50.2 (0.5)	49.9 (0.50)
Male [*n* (%)]	347 (66.6)	361 (69.2)	339 (63.8)	347 (64.3)
Diastolic BP (mmHg)	85.1 (0.4)	85.4 (0.4)	86.1 (0.4)	85.9 (0.50)
Systolic BP (mmHg)	143.8 (0.8)	143.8 (0.8)	144.3 (0.8)	143.8 (0.6)
BMI (kg/m^a)	26.0 (0.2)	25.9 (0.2)	25.6 (0.2)	25.8 (0.2)
Total cholesterol (mmol/l)	6.4 (0.05)	6.5 (0.05)	6.5 (0.05)	6.4 (0.04)
LDL-cholesterol (mmol/l)	4.1 (0.05)	4.2 (0.05)	4.2 (0.04)	4.1 (0.05)
HDL-cholesterol (mmol/l)	1.3 (0.02)	1.3 (0.02)	1.3 (0.02)	1.3 (0.02)
Triglycerides (mmol/l)	2.3 (0.07)	2.3 (0.06)	2.2 (0.06)	2.2 (0.05)
First transplantation (%)	86.8	86.8	84.6	83.7
Total months on renal replacement therapy	57.1 (2.1)	56.6 (1.9)	119.7 (2.2)	120.2 (2.2)
Type of last transplant [*n* (%)]				
Live donor	99 (19.0)	107 (20.5)	130 (24.5)	133 (25.2)
Cadaveric donor	422 (81.0)	415 (79.5)	400 (75.3)	794 (75.0)
Serum creatinine (μmol/l)	142 (2.2)	144 (2.4)	145 (2.4)	150 (2.5)
Traditional and transplant-related risk factors [*n* (%)]				
History of angina pectoris or prior MI	47 (9.0)	45 (8.6)	54 (10.2)	55 (10.4)
Diabetes	102 (19.6)	111 (21.3)	97 (18.3)	86 (16.3)
Hypertension	385 (73.9)	410 (78.5)	392 (73.8)	388 (73.6)
Current smoker	96 (18.4)	103 (19.7)	89 (16.8)	101 (19.2)
HLA DR, two mismatches	75 (14.4)	78 (14.9)	84 (15.8)	91 (17.3)
Panel reactive antibodies	76 (14.6)	69 (13.2)	88 (16.6)	94 (17.8)
Treatment for rejections since last transplantation	208 (39.9)	214 (41.0)	240 (45.2)	240 (45.4)
Delayed graft function	94 (18.0)	82 (15.7)	91 (17.1)	98 (18.6)

[a]Intent-to-treat population.
BP, blood pressure; BMI, body mass index; MI, myocardial infarction.

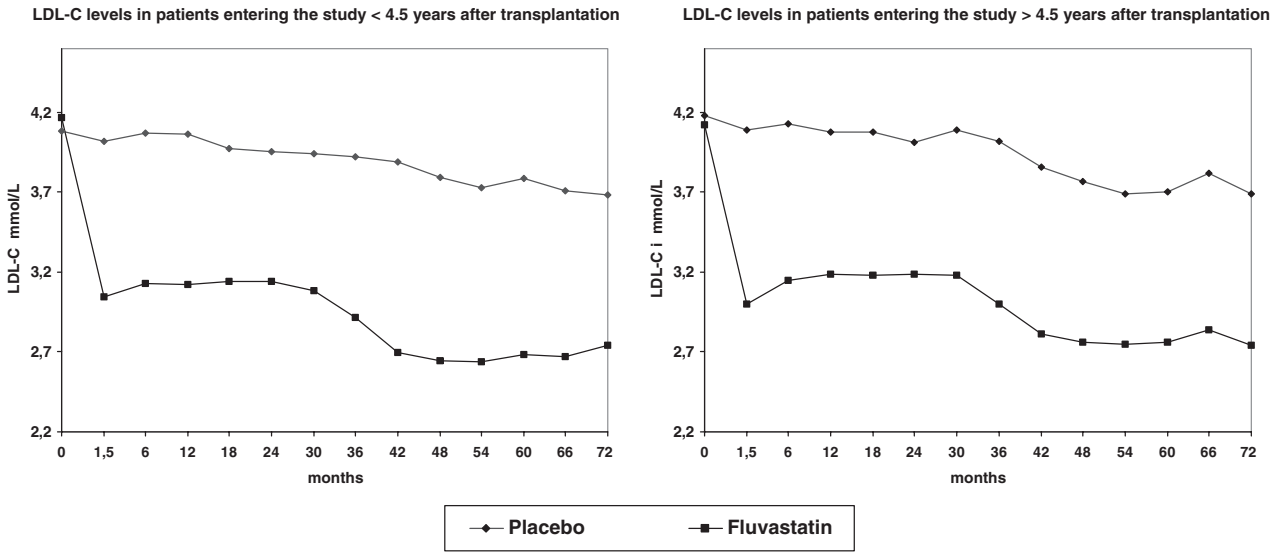
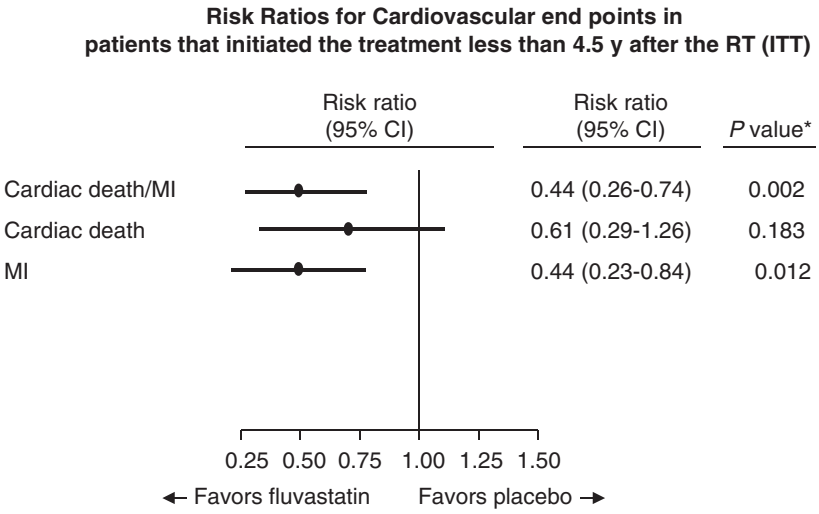


Fig. 1. LDL-cholesterol levels for patients in placebo and fluvastatin arms, entering the trial before and after 4.5 years following renal transplantation.



MI = Non-fatal Myocardial infarction; ITT = intention-to-treat population.
*By Cox proportional hazard model.

Fig. 2. Risk ratio for the composite end-point and the individual components.

Discussion

The ALERT Study [13] is the largest interventional trial in renal transplant recipients and confirmed that the benefit associated with statin treatment observed in the general population is also observed in renal transplant recipients. However, despite compelling evidence that statin therapy is beneficial and reduces the risk of cardiovascular complications, treatment with these drugs has not yet become routine practice following transplantation and in many cases the initiation of statin treatment is delayed until clinical manifestation of hypercholesterolaemia or the occurrence of the first cardiovascular event [15]. In this post-hoc analysis, the importance of the early initiation of the statin therapy became evident. In our analysis, the benefit of treatment with fluvastatin was more evident the earlier the treatment was initiated after transplantation. Different use of potential cardioprotective drugs in the groups could have a confounding effect on outcome measures. However, the use of β-blockers, ACE inhibitors or angiotensin-receptor blockers was not different for any of the groups. Differences in renal function might have had an influence on cardiac end-points. However, no difference in serum creatinine was observed for patients entering the trial early (<4.5 years) or late (>4.5 years) after transplantation. The incidence of cardiac death and non-fatal MI was reduced consistently in patients who started fluvastatin therapy in the first 4.5 years following last

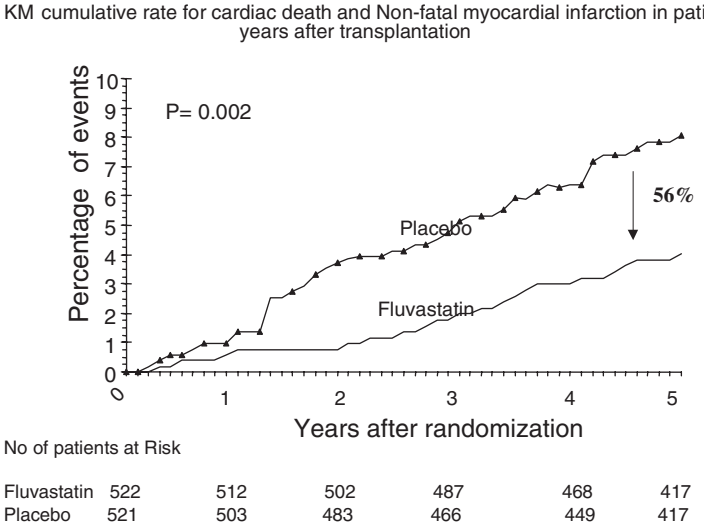


Fig. 3. Kaplan–Meier analysis of survival time free of hard cardiac end-points (cardiac death and non-fatal MI) in patients treated within the 4.5 years after transplantation.

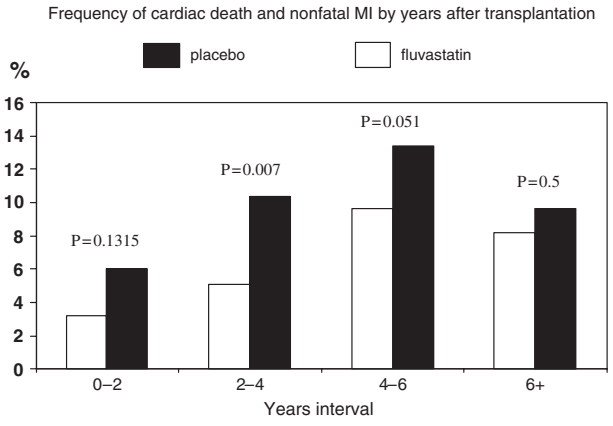


Fig. 4. Frequency of cardiac death or non-fatal MI divided by every 2 year interval after transplantation.

transplantation. On the other hand, those patients who started the therapy later had a smaller, statistically insignificant benefit. The risk of fatal and non-fatal cardiac events was higher in the first 6 years from last transplant in the placebo control group and the risk reduction seen with fluvastatin was larger during this same period. These observations are consistent with the development of irreversible cardiovascular disease with the passage of time following transplantation, or the accumulation of multiple cardiovascular risk factors with time that limit the benefits of intervention on a single risk factor.

We [16] and others have shown that lipid levels rise immediately following transplantation, reaching a maximum after 2–3 months, ~20–30% higher than pre-transplant levels. In one study, 6 months after transplantation the level of total cholesterol exceeded 5.2 mmol/l in 80% of patients and almost all patients had an absolute coronary artery disease risk in excess of 20% over 10 years [17]. The decision to initiate treatment with statins is influenced by several factors. In a recent retrospective study, Cosio *et al.* [18] reported an increased trend in the use of statins in renal transplant patients in the last decade. However, statin therapy was initiated during the first 2 years following transplantation in only 32% of renal transplant recipients; in 20% statins were initiated from the second to the fifth year after transplantation; and in the remainder treatment was initiated later in the post-transplant period. This might reflect the reluctance of many physicians to prescribe statins to transplant recipients due to concerns about potential interactions between some statins and immunosuppressive drugs and about the long-term use of these combinations [19].

The main study report confirmed the safety of fluvastatin in renal transplant recipients on chronic immunosuppressive regimens with no increased risk of malignancy, infection or musculoskeletal complications [13]. The latter are of particular concern because many of the commonly used statin drugs are metabolized by the same microsomal enzymatic pathway (CYP3A4) as calcineurin inhibitors, resulting in greatly increased plasma levels of the statin and the potential for adverse effects. Fluvastatin is not metabolized by CYP3A4 nor is it a substrate of *p*-glycoprotein-mediated transporters [19] and is therefore ideal for use in transplant recipients. This was highlighted by the absence of side effects or adverse effects of fluvastatin (compared with placebo) in the ALERT Study.

Statin therapy is now considered a standard treatment for patients who have had a cardiovascular event and for those who are at equivalent coronary heart disease risk. As a consequence, their use is mandated in clinical guidelines. Renal transplant recipients should be considered in this high-risk group due to the high prevalence of cardiovascular risk factors and high event rates. Although this is an exploratory, post-hoc analysis and the data should not be overinterpreted,

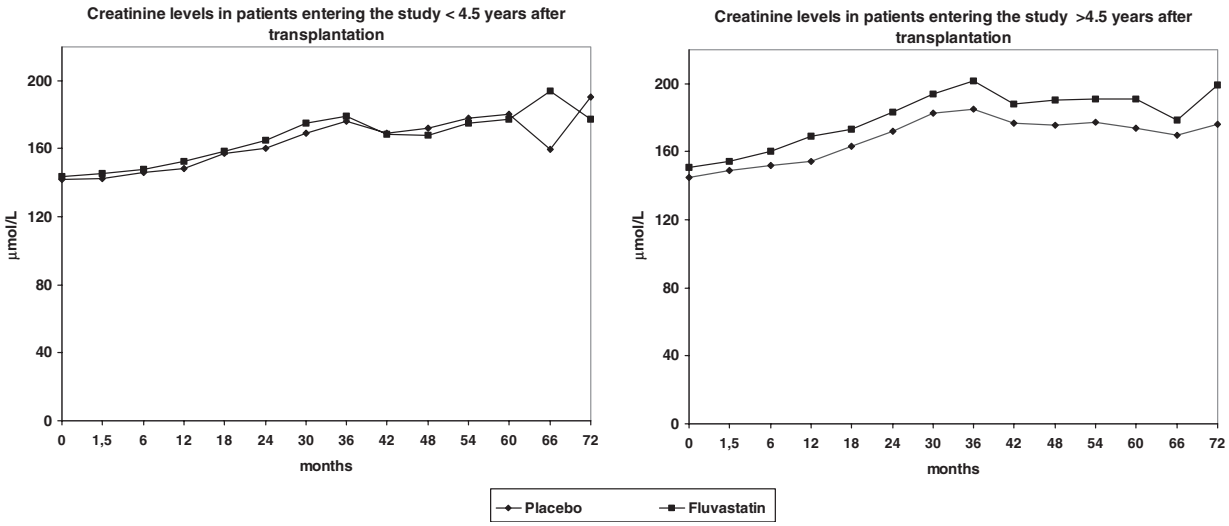


Fig. 5. Creatinine levels for patients in placebo and fluvastatin arms, entering the trial before and after 4.5 years following renal transplantation.

the findings support the increasing use of statins in renal transplantation. The outcome data from ALERT have been pivotal also in supporting the recent recommendation for early and aggressive treatment of dyslipidaemia in renal transplantation by K/DOQI clinical practice guidelines for managing dyslipidaemias in renal transplant recipients [20].

In conclusion, the data in the current post-hoc analysis support the introduction of fluvastatin for treatment of hyperlipidaemia in the early post-transplant period.

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Conflict of interest statement. The ALERT Steering Committee members received financial support from Novartis Pharma AG in the form of honoraria (excluding members who were investigators) and support for travel and accommodation expenses incurred by attending Steering Committee meetings. Members of the Steering Committee have served as consultants for and received travel expenses, payment for lecturing or funding for research from other pharmaceutical companies marketing lipid-lowering drugs, including Merck Shape and Dohme, Bristol-Myers Squibb, AstraZeneka, Schering, Bayer, Pfizer, Fujisawa, Wyeth Ayerst, Genzyme and Hoffman LaRoche. J.O.L., B.S. and C.G. are Novartis employees.

References

1. Briggs JD. Causes of death after renal transplantation. *Nephrol Dial Transplant* 2001; 16: 1545–1549
2. Kasiske BL. Cardiovascular disease after renal transplantation. *Semin Nephrol* 2000; 20: 176–187
3. Lindholm A, Albrechtsen D, Frödin L *et al*. Ischemic heart disease: a major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation* 1995; 60: 451–457
4. Logar CM, Herzog CA, Beddhu S. Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations. *Am J Med Sci* 2003; 325: 214–227
5. Shepherd J, Cobbe SM, Ford I *et al*., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; 333: 1301–1307
6. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–1389
7. Sacks FM, Pfeffer MA, Moye LA *et al*., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335: 1001–1009
8. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339: 1349–1357
9. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7–22
10. Serruys PW, de Feyter P, Macaya C *et al*., for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention. A randomized controlled trial. *JAMA* 2002; 287: 3215–3222
11. Schwartz GG, Olsson AG, Ezekowitz MD *et al*., for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study — a randomized controlled trial. *JAMA* 2001; 285: 1711–1718
12. Cannon CP, Braunwald E, McCabe *et al*. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350: 1495–1504
13. Holdaas H, Fellström B, Jardine AG *et al*. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo controlled trial. *Lancet* 2003; 361: 2024–2031
14. Holdaas H, Fellström B, Holme I *et al*., on behalf of the ALERT Study Group. Effects of fluvastatin on cardiac events in renal transplant patients: ALERT (Assessment of Lescol® in Renal Transplantation) study design and baseline data. *J Cardiovasc Risk* 2001; 8: 63–71
15. Kobashigawa J, Kasiske B. Hyperlipidemia in solid organ transplantation. *Transplantation* 1997; 63: 331–338

16. Holdaas H, Jardine AG, Wheeler DC *et al*. Effect of fluvastatin on acute renal allograft rejection: a randomized multicenter trial. *Kidney Int* 2001; 60: 1990–1997
17. Chmielewsky M, Zdrojewski Z, Rutkowski B. Benefits and menaces related to the use of statins in patients after renal transplantation. *Ann Transplant* 2002; 7: 6–10
18. Cosio FG, Pesavento TE, Pelletier RP *et al*. Patient survival after renal transplantation III: the effects of statins. *Am J Kidney Dis* 2002; 40: 638–643
19. Ballantyne CM, Corsini A, Davidson MH *et al*. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003; 163: 553–564
20. Kasiske B, Cosio FG, Beto J *et al*. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients. A report from The Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant* 2004; 4 [Suppl 7]: 13–53

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